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Modified BFM Protocol for Childhood Acute Lymphoblastic Leukemia: A Retrospective Analysis

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Childhood acute lymphoblastic leukemia (ALL) has a 5-year disease-free survival (DFS) of more than 70%. This fact is not reflected in developing countries due to the lack of proper supportive care. A modified version of the standard Berlin-Frankfurt-Munich (BFM) protocol for pediatric ALL was developed to achieve balance between toxicity and favorable response rates. Modification included a dose reduction of asparaginase and methotrexate during the consolidation and reinduction phase. Forty-two patients younger than 15 years of age were put on the modified BFM protocol between November 1990 and November 1993. Thirty-nine patients were 2–10 years of age and 3 were older than 10 years. Male to female ratio was 3.2:1. 71.4% had L1 and 28.6% had L2 morphology. Univariate analysis factors revealed central nervous system (CNS) involvement and late complete remission (CR) during induction as poor prognostic factors. In multivariate analysis, CNS disease ($P < 0.0083$) was the only prognostic variable for prolonged DFS. All patients went into CR. Eleven patients have relapsed. Life table analysis of these patients shows a 59.4% probability of overall survival (OS) and a 52.5% probability of DFS at 48 months.

Key words: disease-free survival, BFM protocol, CNS involvement

INTRODUCTION

Dramatic improvement in the treatment of pediatric acute lymphoblastic leukemia (ALL) has occurred in the last few decades. Before effective therapy became available, this disease was uniformly fatal with most children surviving only 2–3 months following diagnosis. Currently, with aggressive treatment, greater than 70% of children with ALL achieve prolonged disease-free survival more than 5 years after diagnosis. Most of these patients are considered to be cured.

ALL is a heterogeneous disease. Prognostic factors such as age at diagnosis, sex, cytogenetics, degree of organomegaly, lymphadenopathy, initial leukocyte count, initial hemoglobin level, initial platelet count, FAB morphological classification [1,2], immunophenotype, central nervous system (CNS) disease, presence of glucocorticoid receptors [3], and expression of myeloid antigens can stratify ALL into various risk groups.

Current treatment protocols include remission, induction, CNS preventive therapy, consolidation, and maintenance. Intensive treatment regimens have been developed to improve cytoreduction early during the maintenance phase, especially for patients with poor prognosis [4–7]. The West German Berlin-Frankfurt-Munster (BFM) Group has used the above-mentioned approach to obtain prolonged disease-free survival. Approximately 65–70% of children with poor prognostic factors have achieved prolonged disease-free survival [8].

This high cure rate is not reflected in the developing countries, where only a fraction of children receive state-of-the-art treatment. The major goals in these countries are to induce complete remission and achieve long-term survival rates. However, there are many hurdles in the path to achieving these goals. The expense and complexity of treating ALL and the lack of availability of specialized care are some of the major causes of treatment failures. Patients have to travel long distances to receive chemotherapy and adequate treatment for disease or chemotherapy-related complication. Diagnostic and therapeutic facilities, well-trained personnel, chemotherapentic agents and antibiotics, as well as the necessary supportive services including blood banking and microbiology are all scarce.

Pakistan is a developing country with limited resources. In order to improve survival and increase compliance, we modified the original BFM protocol and reduced the dosage of some drugs in the consolidation and reinduction phase. However, no drugs were deleted from the protocol.

PATIENTS AND METHODS

Patient Selection

A retrospective analysis of 42 consecutive patients was performed over a period of 3 years from November 1990 to November 1993. All previously untreated patients 15 years of age or younger with a diagnosis of ALL were

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included. Pathological subtypes of ALL (L1, L2,) were included.

Evaluation of Disease Status

A complete history, physical examination, hemogram, and hepatic and renal profiles were done, and uric acid and lactate dehydrogenase (LDH) levels were determined. Radiological examination included chest radiographs and abdominal and pelvic ultrasounds. Bone marrow aspirations were performed in all patients and were reviewed by the attending hematologist/oncologist. The diagnosis of acute leukemia was made on H and E stains. Special stains, which included periodic acid-Schiff (PAS), sudan black and myeloperoxidase, were routinely employed to differentiate between ALL and acute nonlymphoblastic leukemia (ANLL). ALL was classified into L1, L2 morphology according to the morphology of lymphoblasts. Lumbar puncture was performed in all patients either on admission or as soon as they had stabilized. Cerebrospinal fluid (CSF) was sent for cell cytology, protein, glucose, and LDH levels.

Febrile patients underwent routine workup of fever if their temperature was greater than 100°F. This included blood cultures, chest X-rays, urinalysis, smears for malarial parasites, and throat cultures. Patients were then started empirically on antibiotics. Chemotherapy was initiated once patients became afebrile or a diagnosis of tumor fever was established.

Chemotherapy

Forty-two patients were placed on the protocol. A schematic overview of the treatment regimen is depicted in Figure 1. The 3-year chemotherapy regimen consisted of five phases of treatment which included induction, consolidation, CNS prophylaxis, reintensification, and maintenance therapy.

Induction therapy consisted of weekly vincristine 1.5 mg/m^2 intravenously (maximum 2mg) and daunorubicin 36 mg/m^2 for 4 weeks. Prednisone 100 mg/m^2 was given continuously for 4 weeks. If bone marrow on day 21 showed greater than 5% lymphoblasts, two additional courses of vincristine and daunorubicin, in the same dosage, were given. Bone marrow aspirate was then repeated on day 36.

The consolidation phase consisted of L-asparaginase 6,000 units/m^2 three times a week for a total of nine doses. Cyclophosphamide 1,200 mg/m^2 was given on weeks 10–12 and 14. Concomitantly cytosine arabinoside 100 mg/m^2 was started for 4 days every week for a total of 6 weeks.

Reintensification started on week 20 with vincristine 1.5 mg/m^2 and daunorubicin 36 mg/m^2 given intravenously weekly for 2 weeks. Prednisone was also given in a dose of 60 mg/m^2 daily for 2 weeks. This was followed by intermediate dose methotrexate 500 mg/m^2 with folinic

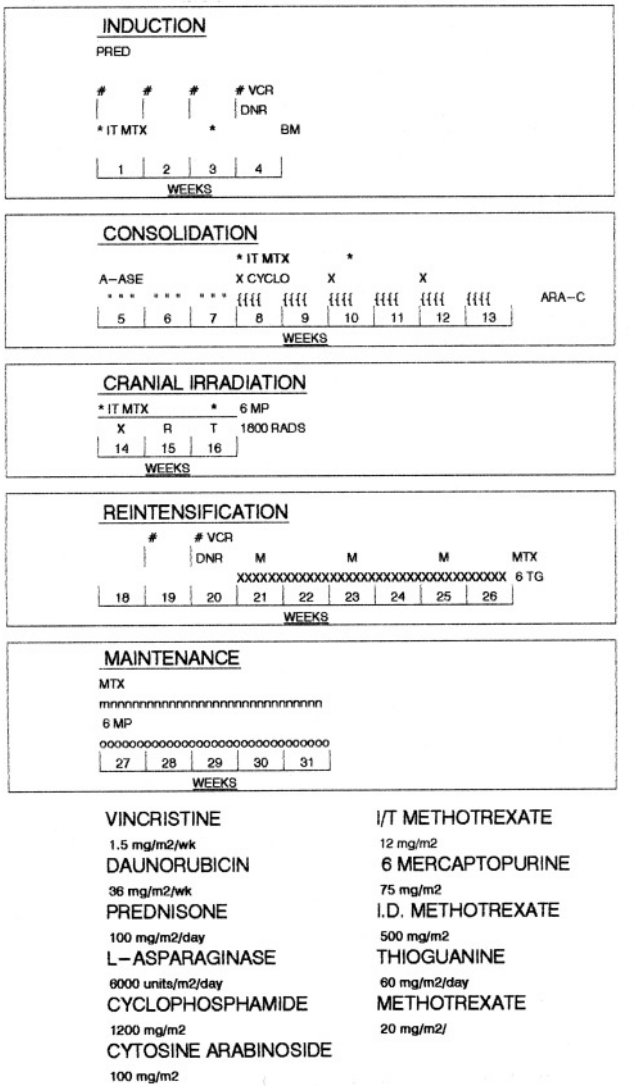

Fig. 1. Modified BFM Protocol for pediatric ALL.

acid rescue given on weeks 22, 24, and 26. 6-Thioguanine 60 mg/m^2 was given daily from week 22 to 26.

Maintenance therapy consisted of oral 6-mercaptopurine 75 mg/m^2 daily and oral methotrexate 20 mg/m^2 once weekly. Vincristine 1.5 mg/m^2 and prednisone 60 mg/m^2 were given every 4 weeks during maintenance therapy. The duration of maintenance therapy was 30 months.

CNS prophylaxis began during induction therapy with intrathecal methotrexate 12 mg/m^2 given on weeks 0, 2, 8, 10, 14, and 16, followed by the same dose every 8 weeks for a total period of 2 years. Cranial radiation was given prophylactically to every patient starting from week 14 to week 16. Oral 6-mercaptopurine 75 mg/m^2 was given daily from week 14 to 20. In patients with established disease, intrathecal methotrexate 12 mg/m^2 was given two times per week till CSF cytology became negative. Following that, intrathecal methotrexate was given

every 4 weeks for 6 months and then every 6 weeks for a total duration of 2 years.

All patients underwent a prophylactic or therapeutic cranial irradiation of 1,800 rad during the consolidation phase as specific in the protocol. There were no patients younger than 2 years of age.

Statistical Analysis

Statistical analysis was performed on SPSS/PC+. Univariate analysis and multiple logistic regressions were performed on age, sex, CNS disease, hepatosplenomegaly, hemoglobin level, white blood cell (WBC) count, platelet count, bone marrow morphology and rapid early remission (RER) during induction therapy. Chi-square analysis was done and Fisher's exact test was applied where necessary. Life table analysis for overall survival and disease-free survival was calculated according to Kaplan-Meier survival curves.

RESULTS

Patient Characteristics

Data on 42 patients were evaluated. Table I indicates important patient characteristics, laboratory features, and FAB morphology at diagnosis. There was significant male predominance. Thirty-nine (92.9%) patients were between 2 and 10 years of age and 3 (7.1) were older than 10 years. No patient was less than 2 years of age. Thirty-five percent of the patients belonged to the poor class, 50% belonged to the middle class, and only 15% were from the upper socioeconomic stratum. Poor socioeconomic status was defined as a per capita income of less than Rs.2000/-per month, middle socioeconomic status had an income between Rs.2000/- and Rs.5000/-, and high socioeconomic group had an income above Rs.5000/-.

Pallor was present in 100% of cases. 78.3% had malaise, 52.4% complained of bone pains, and 33.3% of patients had a bleeding diathesis on presentation. Fever was present in all of the patients and infection was documented in 76.2%. The most common infection seen was pneumonia. After the relevant laboratory investigations, a diagnosis of tumor fever was made in 10 (23.8%) patients.

Bone marrow examination revealed L1 morphology in 30 (71.4%) and L2 in 12 (28.6%) patients. Fifteen of 42 patients (35.7%) had CNS disease on presentation. It was documented by the presence of leukemic blasts on CSF cytology. Lymph node enlargement of 1 cm or greater was seen in 35 (83.3%) patients. Hepatosplenomegaly was present in 24 (57.1%) patients (a liver span more than 8 cm and a palpable spleen 3 cm below the coastal margin were considered positive). There was no testicular involvement in any of the patients.

All patients had an initial hemoglobin level of less than 10 g/dl with 23 (54.8%) patients having a hemoglobin level of less than 5 g/dl. Initial WBC count was less than 20,000 in 25 (59.9%) patients but greater than 20,000 in 17 (40.5%) patients, of whom 8 had a count of greater than 100,000. Platelet count was less than 100,000 in all patients and less than 20,000 in 16 (38.1%). LDH levels were raised (>400 IU/L) in 33 (79.2%) patients. The liver profile was considered abnormal in patients with serum transaminases $1\frac{1}{2}$ times the normal value. An abnormal liver profile was documented in 11 (26.1%) patients. All patients with an abnormal liver profile underwent a hepatitis screen for hepatitis B and C viruses. Three patients had an abnormal renal profile with a serum creatinine level of more than 2 mg/100 ml. One patient had a raised serum uric acid level (>8.5 mg/100 ml).

TABLE I. Clinical and Laboratory Features at Diagnosis of Children With ALL (n = 42)

Clinical/laboratory features	No. Patients (%)
Patient characteristics	
Total number of patients	42 (100)
No. of patients evaluable	42 (100)
Males	32 (76.2)
Females	10 (23.8)
Male:female ratio	3.2:1
Age distribution (years)	
2–10	39 (92.9)
>10	3 (7.1)
Symptoms and physical findings	
Fever	42 (100)
Pallor	42 (100)
Malaise	33 (78.6)
Bone pains	22 (52.4)
Bleeding diathesis	14 (33.3)
Lymphadenopathy	35 (83.3)
Hepatosplenomegaly	24 (57.1)
CNS involvement	15 (35.7)
Laboratory features	
hemoglobin (g/dl)	
<5	23 (54.8)
5–10	19 (45.2)
WBC	
<20,000	25 (54.8)
>20,000	17 (40.5)
Platelets	
<20,000	16 (38.1)
>20,000	26 (61.9)
LDH	
Normal	9 (20.8)
High	33 (79.2)
Morphological subtype	
L1	30 (71.4)
L2	12 (28.6)

Correlation of First Complete Remission With Prognostic Factors

Thirty (71.4%) patients placed on the protocol achieved RER as assessed by bone marrow examination on day 21 of induction therapy. Twelve (29.6%) patients achieved late remission as seen on bone marrow examination on day 36 and received additional two courses of induction therapy. All patients eventually went into complete remission. Early remission in our study was associ-

TABLE II. Prognostic factors in patients achieving event-free survival (n = 25)

Variable	No. of patients	*P*
Age (years)		
2–10	24	0.21
>10	1	
Sex		
Male	17	0.16
Female	8	
Morphological subtype		
L1	18	0.43
L2	7	
Hepatosplenomegaly		
Yes	12	0.25
No	13	
CNS involvement		
Yes	4	0.0036
No	21	
Complete remission		
Early	21	0.048
Late	4	

ated with a favorable prognosis and correlated significantly with survival ($P = 0.048$).

Chi-square analysis of all patients achieving RER was performed with regard to various prognostic factors. These included age, sex, morphological subtype of disease, hemoglobin level, WBC count, platelet count, LDH level, hepatosplenomegaly, lymphadenopathy, and CNS involvement. Age was not a significant prognostic factor ($P = .1496$). Male sex, L2 morphology, hepatosplenomegaly, and CNS involvement were significant prognostic factors in achieving early complete remission (see Table II for *P* values).

Correlation of Disease-Free Survival With Prognostic Factors

Univariate analysis of various prognostic indicators was performed. This included age, sex, bone marrow morphology, hepatosplenomegaly, CNS disease, and RER vs. late complete remission. The only significant prognostic factors identified were CNS disease ($P < 0.0036$) and RER ($P < 0.048$).

Multiple logistic regression was performed on the prognostic factors mentioned above. CNS disease was the only significant prognostic indicator for achieving prolonged disease survival ($P = 0.0083$).

Patient Follow-up

Forty-two patients were evaluated for their response to chemotherapy. All patients achieved complete remission with 30 (71.4%) achieving early remission. Patient compliance was excellent and the drugs were given at the doses indicated in the protocol. In case of infections, therapy was delayed until the patient was stabilized. However, no drug modification or omission of drugs took place.

A total of 17 patients expired. Eleven patients relapsed, nine of whom were on chemotherapy. Two patients relapsed within the first year of stopping therapy. All those who relapsed later expired. Treatment-related mortality included sepsis in five patients and uncontrolled bleeding in one. This occurred during the consolidation phase. All patients were in complete remission.

Currently 25 (59.5%) patients are alive and in complete remission. The median duration of follow-up is 26.5 months. According to the life table analysis, cumulative probability of overall survival is 59.4% and that of disease-free survival is 52.5% at 48 months. Figure 2 shows disease-free survival and overall survival of all patients.

Relapsed Disease

A total of 11 patients relapsed, 9 of whom were on chemotherapy and 2 of whom were off chemotherapy. These nine patients relapsed after being on chemotherapy for a median of 29 months. Two patients had recurrence of disease in the bone marrow, six patients had recurrence both in the CNS and bone marrow, and one patient had a testicular relapse. The two patients who were off chemotherapy relapsed within the first year of stopping therapy and had disease recurrence in the bone marrow and CNS. Nine patients relapsed on chemotherapy, of whom 8 had L2 subtype disease and eight were males. All relapsed patients had two or more poor prognostic factors identified earlier. Of the 11 patients who relapsed, 9 had late remission out of a total of 12 patients achieving late remission (75%). Only 2 (6.6%) patient who achieve early remission relapses out of a total of 30 patients ($P < 0.01$).

Toxicity

Five patients died during treatment as a result of treatment-related sepsis which included gram-negative septicemia in four patients and herpes encephalitis in one patient. Intracranial bleeding was the cause of death in one patient.

Nonfatal toxicity was mainly hematological (absolute neutrophil count <500/cm and/or platelet count <30,000/cm). Life-threatening bacterial infection occurred during periods of neutropenia and needed aggressive antibiotic support. One patient developed grade III hepatic encephalopathy due to L-asparginase which was nonfatal.

DISCUSSION

Current therapy for ALL is producing 86% and 71% 5-year event-free survival for standard and high-risk patients, respectively [10,11]. Unfortunately, these results are not seen in developing countries where survival rates are exceedingly low and very few reports are available on the use of different protocols. This is further complicated by poor follow-up rates. The chemotherapeutic protocols used in developed countries require excellent supportive care that must be implemented parri passu with chemotherapy protocols. In addition, there are environmental influences including poor nutritional status, differ-

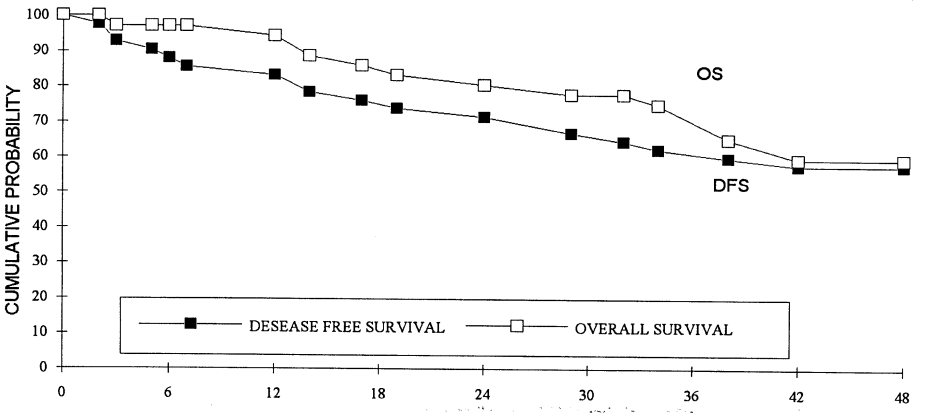

Fig. 2. Kaplan Meier Survival estimates on overall survival (OS) and disease free survival (DFS).

ent spectrum of infectious agents including latent infections, and socioeconomic problems. These do not allow very aggressive protocols to be followed in less developed countries as this may contribute to significant morbidity and mortality. Once efficacy of a protocol is established, it is difficult to justify using a less aggressive protocol. Keeping in mind the constraints of the developing countries, we decided to modify the original BFM protocol so that it would allow adequate supportive care facilities and proper administration of chemotherapeutic drugs with minimum burden to the family. We did not initially attempt to categorize patients into standard or high-risk groups as we were unsure of patient compliance with very aggressive regimens. The majority of patients travel long distances to receive chemotherapy. Infections and other complications would be difficult to handle by parents or physicians not familiar with modern oncological practice, leading to increased morbidity and mortality.

The dose of methotrexate was reduced to 500 mg/m^2 due to lack of availability of methotrexate levels. Initial experience with 10,000 units/m^2 of asparaginase led to grade 3 or 4 hepatotoxicity in two patients. We therefore reduced the dosage of asparaginase to 6,000 units/m^2. All 42 patients put on our protocol were evaluable for analysis. The significant male predominance is probably related to our cultural peculiarities where males are provided with more health care facilities than females. This is especially true for middle and lower socioeconomic groups. The presenting signs and symptoms and hematological abnormalities are similar to those reported in the western literature [12]. The reported incidence of CNS leukemia at diagnosis occurs in fewer than 5% of children [13]. In our series 35.7% children had CNS disease on presentation as documented by positive CSF cytology [14–17]. This may be related to a delay in diagnosis as the majority of the patients were treated for infectious diseases and nutritional anemias by their treating physicians before a diagnosis of leukemia was made.

The following prognostic factors were evaluated retrospectively. These included age [18], sex [19], initial leukocyte count, initial hemoglobin level, platelet count, FAB morphological classification, CNS involvement, and attainment of RER as assessed by bone marrow morphology on day 21 [19–22]. More sophisticated prognostic factors like immunophenotyping and glucocorticoid factors could not be evaluated, either because of lack of availability of these tests or required specialized laboratory facilities not being available in our institute. Poor prognostic factors identified in our study for RER were male sex. L2 morphology, hepatosplenomegaly, and CNS involvement on presentation. Age as a poor prognostic factor was not significant. We recognize that in a small study some factors that have prognostic influence may not be able to achieve a traditional ($P = 0.05$) significance level.

Complete remission was achieved in 100%, 71.4% of which achieved early remission. All patients received full doses of chemotherapy. However, treatment delay occurred in febrile neutropenic patients. The average delays in treatment was 8–10 days. The use of growth factors in febrile neutropenic patients shortened the duration of neutropenia to 4–5 days. Septicemia was the major cause of death (12.5% of patients) which occurred during the consolidation and reintensification phase [23]. The high mortality in this period was related to a delay in supportive treatment as the patients came late. With improved patient education, more aggressive follow-up, and judicious use of hematopoetic growth factors during periods of severe neutropenia, life-threatening septicemia has decreased. All patients who died were in complete remission.

Eleven patients relapsed on this protocol. Nine of these 11 patients had achieved late complete remission [24,25]. Male sex and L2 morphology were present in 9 of 11 patients achieving late complete remission. The high incidence of relapses in the maintenance phase is significant. The reasons are multifactorial; lack of compliance by the patients diminishes the efficacy of maintenance therapy [26]. In order to exclude compliance problems, we are closely monitoring patients during maintenance. Bioavailability of oral methotrexate and 6-mercaptopurine may be limited and highly variable, accounting for some treatment

failures [27,28]. Unfortunately, we do not have sophisticated laboratory facilities to measure drug levels. The incidence of infectious complications in developing countries is high due to water, food, and environmental contamination, frequently necessitating interruptions in maintenance schedules [29]. This may contribute to the relatively high relapse rate seen in our study during maintenance.

Patients who achieved late complete remission and those with CNS disease on presentation may benefit from more aggressive protocols in order to achieve prolonged disease-free survival. Poor prognostic factors can also be identified by simple means if sophisticated laboratory technology is not available.

The cumulative probability of overall survival and disease-free survival at 48 months is 59.4% and 52.5%, respectively. Since we had not stratified patients into different risk groups, the probability of survival may be higher if only standard risk patients are put on this protocol. In the light of our results, we recommend treating our patient population with the modified version of the BFM protocol. Higher-risk patients, male sex, L2 morphology, CNS disease, and late remission should be treated with more aggressive and unmodified protocols.

In conclusion, various constraints and problems of developing countries need to be identified and patients should receive maximum treatment with minimum toxicity without compromising cure in childhood leukemia. Our study reveals that close follow-up and proper management can achieve cures in patients in the less developed countries. We are now prospectively allocating patients into standard and high-risk groups and giving treatment accordingly.

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